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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket No. 2004Q-0180; Qualified Health Claim – Lutein and Eye Diseases

ZeaVision LLC (ZeaVision) submits these comments concerning the proposed qualified health claim for lutein and age-related macular degeneration (AMD) and cataract formation. Although the comment period for the lutein petition has now closed, we write to underscore the need—as suggested by previous commenters—for FDA to consider the unique relationship between zeaxanthin and lutein as the agency evaluates the proposed claim for lutein esters. The proposed health claim cannot be fully and fairly evaluated without express consideration of zeaxanthin, and the scientific evidence presented for lutein and lutein esters also supports a claim for zeaxanthin and zeaxanthin esters.

A claim for zeaxanthin is supported by the following key considerations:

- Lutein and zeaxanthin are jointly present at meaningful levels in many conventional foods and all lutein supplements. Accordingly, at a minimum, the beneficial effects attributed to lutein in the petition can be attributed in part to zeaxanthin.
- The biological and other properties of zeaxanthin provide a basis upon which zeaxanthin may be reasonably concluded to provide protection that equals or surpasses that conferred by lutein:
 - Dietary zeaxanthin has been shown to increase macular pigment density, which is inversely associated with AMD risk.

- Studies have repeatedly shown that zeaxanthin is preferentially incorporated into the center of the macula—an area of critical importance to sight.
- The chemical structure and antioxidant capacity of dietary zeaxanthin are ideally suited to protect against eye diseases such as AMD and cataract.

ZeaVision requests that FDA exercise enforcement discretion and allow, in addition to an appropriate claim for lutein and/or lutein esters, a claim for dietary zeaxanthin and/or its esters. The basis for this request is described more fully below.

ZEAXANTHIN ACCOMPANIES LUTEIN IN MANY FOODS AND ALL LUTEIN SUPPLEMENTS

Lutein and zeaxanthin, and their esters, coexist in many foods, including dietary supplements. Many conventional foods that are among the best sources of lutein (e.g., spinach, corn) are also rich in zeaxanthin. In addition, all commercially produced “lutein” contains zeaxanthin because zeaxanthin is included when marigolds are processed for lutein. The zeaxanthin content of “lutein” supplements is generally 5%; zeaxanthin is present at a concentration of < 7% in the lutein esters that are the subject of the proposed health claim. 1/ The close relationship between zeaxanthin and lutein is expressly acknowledged in the qualified health claim petition, which repeatedly references “lutein and zeaxanthin” in describing the scientific literature.

Because lutein and zeaxanthin are found jointly in so many foods, including dietary supplements, it is not possible to fully and fairly evaluate a claim for lutein without also giving consideration to zeaxanthin. Indeed, at a minimum, the body of research that supports a lutein claim likewise supports a claim for zeaxanthin. For this reason, both zeaxanthin and lutein (as separate ingredients) are expected to be new components in the formulation to be examined in the upcoming Age-related Eye Disease Study (AREDS II). 2/ At the 2004 meeting of the Association for Research in Vision and Ophthalmology (ARVO) (poster #2242,) a presentation on

1/ Although lutein is almost always accompanied by zeaxanthin, the reverse is not necessarily true: pure commercial dietary 3R,3R' zeaxanthin contains no lutein. Therefore, although commercial lutein generally cannot be manufactured without some zeaxanthin content, zeaxanthin can be produced as an isolated carotenoid.

2/ Neither dietary 3R,3R' zeaxanthin nor lutein was commercially available when the original AREDS formulation was created during the early 1990's.

AREDS participants concluded that a higher intake of zeaxanthin and lutein were associated with a decreased likelihood of having advanced AMD at baseline.

Although lutein is far more prevalent in the diet and in lutein supplements than zeaxanthin, the significance of zeaxanthin, even at relatively lower levels, cannot be discounted. As explained next, the molecular structure and the biological properties of zeaxanthin provide a basis upon which this carotenoid may be reasonably concluded to provide protection that equals or surpasses that conferred by lutein.

DIETARY ZEAXANTHIN HAS BEEN SHOWN TO INCREASE MACULAR PIGMENT DENSITY

Numerous studies (Bone et al. 2003, Hartmann et al. 2004, Garnett et al. 2002) have shown that increased blood levels of dietary 3R,3R' zeaxanthin from a variety of sources result in increased macular pigment density, which in turn has been inversely associated with AMD risk. Bone et al. 2003 demonstrated that the ability to modify macular pigment optical density (MPOD) is directly related to peak blood serum levels. Garnett et al. suggested zeaxanthin to have better retinal uptake than lutein.

The relationship between macular pigment density and disease risk was most recently addressed in a scientific presentation (ARVO 2004, poster #2967/B602) regarding macular pigment optical density and serum and dietary lutein and zeaxanthin in healthy subjects with and without a family history of Age-Related Maculopathy. The researchers concluded that in the absence of retinal pathology, the relative lack of macular pigment among smokers and subjects with a confirmed family history of ARM supports the hypothesis that a deficiency of macular carotenoids (zeaxanthin and lutein) may predispose to AMD.

Some authors have suggested that zeaxanthin may play a unique role in mitigating AMD risk. In a recent observational study, Gale et al. 2003 found the risk of AMD to be significantly higher in individuals with low levels of serum zeaxanthin, but not those with low levels of lutein. The authors reasoned that "[our] finding that plasma zeaxanthin, but not plasma lutein, is significantly [inversely] associated with risk of age-related macular degeneration suggests that their roles may not be identical." The authors further suggested that the practice of analyzing the combined concentration of lutein and zeaxanthin "may have obscured evidence of zeaxanthin's protective role."

ZEAXANTHIN IS PREFERENTIALLY INCORPORATED INTO THE MACULA'S CENTER

The relative importance of zeaxanthin to lutein is further supported by studies indicating that dietary 3R,3R' zeaxanthin is preferentially incorporated into the very center of the macula—the area of the macula most important to central sight (Bone et al. 1988, Snodderly et al. 1991). ^{3/} This preferential uptake occurs even though lutein is far more common in the diet and in plasma. The ratio of dietary lutein to dietary zeaxanthin is between 5 to 20:1; the ratio of plasma lutein to plasma zeaxanthin is between 3 to 5:1. The ratio in the center of the macula, however, is approximately 2:1 zeaxanthin to lutein, which strongly indicates the preferential uptake of zeaxanthin by the eye.

Zeaxanthin is also preferentially incorporated into the lens. Yeum et al. 1995 demonstrated that zeaxanthin and lutein are the only two carotenoids found in the human lens. Khachik et al. 2002 found the ratios of lutein to dietary 3R,3R' zeaxanthin in the lens to be approximately 1.5:1, which suggests a preferential uptake for dietary 3R,3R' zeaxanthin from the diet (where the ratio is between 5 to 20:1) and plasma (where the ratio is 3 to 5:1) to the lens (where the ratio is 1.5:1.)

In addition, a study by Berendschot et al. 2002 concludes that there is an *inverse* relationship between Lens Optical Density and Macular Pigment Optical Density. For complex reasons, that unexpected result indicates if the *macula* cannot obtain enough zeaxanthin and/or lutein, then the *lens* tries to compensate for that problem and protect the macula, by sequestering as much of those two pigments as it can. This unusual result, and the mechanisms behind it, strongly suggest that zeaxanthin and lutein, in the lens, play crucially important protective roles in human eyes.

ZEAXANTHIN HAS UNIQUE PROPERTIES THAT MAY PROVIDE SUPERIOR PROTECTION

The chemical structure of zeaxanthin and its likely antioxidant activity suggest that zeaxanthin is ideally suited to provide protection at least equal to, and most likely better than, lutein. The unique properties of zeaxanthin help to explain why this carotenoid is favored in the center of the macula (Sujak et al., 1999 and 2002).

^{3/} The importance of the central area of the macula is underscored by the process of Central Sparing, which was described by Weiter et al. In Central Sparing, cell death in macular degeneration is reasoned to begin at the peripheral portion of the macula and move inward toward the center over time, presumably “sparing” the critical central region.

Sujak et al. found stereochemical and structural differences between dietary 3R,3R' zeaxanthin and lutein and differences in their protective activity. Significantly, dietary 3R,3R' zeaxanthin's eleven (11) conjugated double bonds throughout the molecule, versus ten (10) for lutein, allow for zeaxanthin to have a higher quenching ability for reactive species than lutein. Conjugated double bonds are particularly effective at quenching singlet oxygen that produces Reactive Oxygen Species (ROS), and are also effective at absorbing harmful UV rays.

Dietary 3R,3R' zeaxanthin can also adopt a more favorable membrane spanning position relative to lutein, lending itself to enhanced photoprotection.

Two recent studies by Wrona and coworkers showed that dietary 3R,3R' zeaxanthin acted synergistically with α -tocopherol and/or ascorbic acid to protect liposomes from lipid peroxidation induced by photodynamic damage, as well as protecting retinal pigment epithelial cells (RPE) against photo-induced oxidative stress. These experiments, although *in vitro*, support the theory that zeaxanthin may be a stronger antioxidant than lutein. Ocular lipid peroxidation and RPE oxidative stress are believed to be directly related to macular degeneration.

In summary, zeaxanthin may reasonably be concluded to provide protection that is equal to, if not better than, lutein. This conclusion is based upon the advantageous chemical structure dietary 3R,3R' zeaxanthin has relative to lutein, its superior antioxidant activity, the body's preferential uptake of dietary 3R,3R' zeaxanthin, and the central sparing of the macula. 4/

DIETARY ZEAXANTHIN IS SAFE

The safety of zeaxanthin in supplements has been confirmed by a New Dietary Ingredient Notification for dietary 3R,3R' zeaxanthin. The notification was filed by Roche Vitamins and was reviewed by FDA without objection in 2001 (see Docket No. 95S-0316: 75-Day Premarket Notifications for New Dietary Ingredients, Report No. 96).

In addition, the Joint Food and Agriculture Organization/World Health Organization (FAO/WHO) Expert Committee on Food Additives (JECFA) recently completed a toxicological evaluation of zeaxanthin. JECFA established a group Acceptable Daily Intake (ADI) for lutein and zeaxanthin of 0-2 mg/kg bw for zeaxanthin (see JECFA, Summary and Conclusions, 63rd meeting, Geneva June

4/ There are also direct animal data (Thompson et al. 2002) demonstrating retinal protective effects of dietary zeaxanthin.

2004). For example, a 150 lb. individual could safely consume up to 136 mg (daily) of zeaxanthin and lutein, and a person weighing 200 lbs could consume up to 181 mg of zeaxanthin and lutein, according to this assessment.

DIETARY ZEAXANTHIN DOES NOT INCLUDE MESO-ZEAXANTHIN

The above conclusions concerning dietary zeaxanthin do not apply to meso-zeaxanthin, a non-dietary stereoisomer of the nutrient zeaxanthin. Meso-zeaxanthin, which is not found in plasma or other tissues, is generally understood to be present only in the eye as a result of its synthesis from lutein. It has been hypothesized to result from the conversion of lutein, in the eye, in response to the body not receiving an adequate amount of dietary 3R,3R' zeaxanthin. An intermediate form of non-dietary zeaxanthin, meso-zeaxanthin is best described as a compromise structure to the more preferred dietary 3R,3R' zeaxanthin.

REQUESTED CLAIMS

On the basis of this information, ZeaVision requests that FDA exercise enforcement discretion and allow, in addition to any appropriate claim for lutein and/or lutein esters, the following claim concerning reduced risk of AMD and cataract and zeaxanthin or zeaxanthin esters:

Consumption of 6 mg of zeaxanthin may reduce the risk of age-related macular degeneration and cataract formation. FDA has determined that the evidence is supportive, but not conclusive, for this claim. This food/dietary supplement provides ___ mg of zeaxanthin per serving.

As reflected in this suggested claim, ZeaVision agrees with the petitioner's conclusions that 6 mg per day is a desirable daily intake of lutein, and thus zeaxanthin, for purposes of reducing AMD and cataract risk. For a consumer-friendly claim, however, we recommend that the language be phrased in terms of active "zeaxanthin and/or lutein."

* * *

In summary, it is our contention that dietary 3R,3R' zeaxanthin and/or zeaxanthin esters have, to a greater or lesser degree, participated in every major lutein study because they are inherently included through either diet or the commercial production of lutein. Therefore, it seems impracticable and inappropriate to consider lutein for a health claim without including zeaxanthin. Furthermore, there is sufficient evidence to reach a logical conclusion that zeaxanthin may well be

equal to or better than lutein, relative to their protective roles in the human body, providing additional support for a zeaxanthin claim.

Thank you for your consideration of these comments.

Sincerely,



Dennis Gierhart, Ph.D.
Chairman and CEO
ZeaVision LLC

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